CILJEVI ANALITIČKE KVALITETE IZ NOVE PERSPEKTIVE

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Klinički zavod za medicinsku biokemiju i laboratorijsku medicinu,
Referentni centar Ministarstva zdravstva za Republike Hrvatske
za izradu i primjenu bioloških referentnih intervala
medicinskobiokemijskih pretarga, Klinička bolnica Merkur, Zagreb

15189·HAA

7130

Tečaj trajne edukacije „Primjena biološke varijacije u laboratorijskoj medicini”

Zagreb, 11.-12.12.2021.

Sljedivost u laboratorijskoj medicini

Laboratory users expect laboratory results to be equivalent, no matter where and how they are obtained, and interpreted in a consistent way

STANDARDIZATION

Unbroken traceability chain

Definition of higher-order references to implement the appropriate trueness transfer process to commercial calibrators and patient results

Measurement uncertainty

With definition of allowable limits for clinical application of the measurements

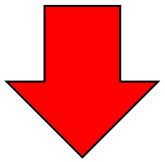
Post-market surveillance

Survey the suitability of IVDs for clinical use and of laboratory performance in using them through appropriate quality control programs

Panthegini M. et. al. Clin Chem. 2021;67:1590-1605.

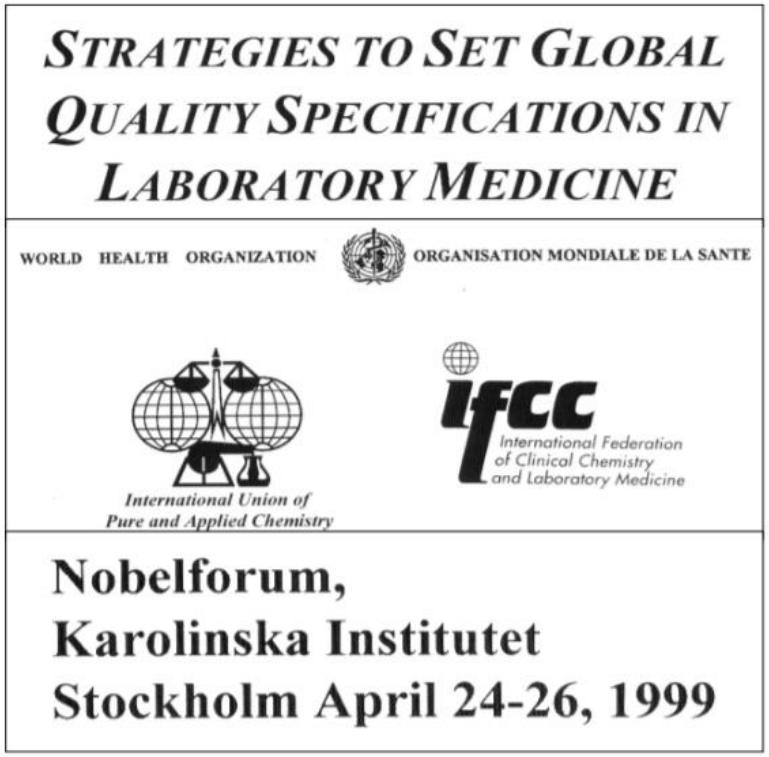
- ✓ Veličina analitičke pogreške ne smije utjecati na kliničku interpretaciju rezultata laboratorijskih pretraga
- ✓ Kroz sustav kontrole kvalitete osigurati da svaka pretraga zadovolji postavljene kriterije prihvatljivosti

Kako procjeniti i odrediti dozvoljenu veličinu analitičke pogreške ?



Kako definirati analitičke ciljne vrijednosti za preciznost, točnost, ukupnu analitičku pogrešku i mjernu nesigurnost?

Međunarodni sporazumi za definiranje ciljeva analitičke kvalitete



Stockholmski sporazum (1999.g.)

DE GRUYTER

Clin Chem Lab Med 2015; 53(6): 837–840

Opinion Paper

Callum G. Fraser*

The 1999 St … quality spe… … e on … ne

DOI 10.1515/cclm-2014-0914
Received September 17, 2014; a…
published online February 7, 201…

Abstract: The setting of a… in laboratory medicine ha… and debate for over 50 yea… matured and a profusion … many of them from exper… number of leading professi… a global consensus on the… The Stockholm Conference … set global analytical quali… medicine" achieved this a… application of a hierarchica…

The consensus statement

The main outcome of the consensus conference was agreement that the following hierarchy of models should be applied to set analytical quality specifications.

1. Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings.
2. Evaluation of the effect of analytical performance on clinical decisions in general:
   a. Data based on components of biological variation,
   b. Data based on analysis of clinicians' opinions.
3. Published professional recommendations:
   a. From national and international expert bodies,
   b. From expert local groups or individuals.
4. Performance goals set by:
   a. Regulatory bodies,
   b. Organisers of EQA schemes.
5. Goals based on the current state of the art:
   a. As demonstrated by data from EQA or Proficiency Testing schemes,
   b. As found in current publications on methodology.

… ars that it is impos-
… uss quality in labo-
… ality specifications
… nce goals) are set a
… at objective analyti-
… ed so that adequate
… cations are required
… drawing up specifi-
… thodology or equip-
… lates, in evaluation
… erformance charac-
… id to set up quality
… vidual laboratories;

Milanski sporazum (2014.g.)

DE GRUYTER Clin Chem Lab Med 2015; 53(6): 833–835

Consensus Statement

Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

Consensus statement

Analytical performance specifications

In this revision, the hierarchy is simplified and represented by three different models to set analytical performance specifications. There is general agreement that some of these are better suited for certain measurands than for others.

Model 1- temeljen na utjecaju karakteristika analitičke izvedbe na klinički ishod

1a. Direktne studije kliničkog ishoda – ispituju utjecaj karakteristika analitičke izvedbe na klinički ishod

1b. Indirektne studije kliničkog ishoda – ispituju utjecaj karakteristika analitičke izvedbe na kliničku klasifikaciju ili kliničku odluku i time na vjerojatnost kliničkog ishoda

Prednost: o analitičkim karakteristikama izvedbe ovisi klinički ishod, pa je model usmjeren na potrebe pacijenata i društva u cjelini

Nedostatak: odnosi se na mali broj pretraga kod kojih postoji izrazitao jaka povezanost pretrage i kliničke odluke

Model 2- temeljen na komponentama biološke varijacije

- ✓ nastoji se smanjiti utjecaj analitičke varijacije na biološku varijaciju

Prednost: može se primjeniti na vrlo velik broj pretaraga za koje je određena biološka varijacija

Nedostatak: nestandardizirana izrada komponenata biološke variajcije zbog čega su prisutne značajne varijacije u dostupnim literaturnim podacima

Model 3- temeljen na aktualnom stanju struke

- ✓ Odnosi se na najvišu razinu analitičke izvedbe koja se može postići primjenjenom tehnologijom ili se može definirati kao razina analitičke izvedbe koju može postići najviši udio laboratorija

Prednost: dostupni su podaci za sve klinički relevantne pretrage

Nedostatak: moguća nepovezanost analitički mogućeg i optimalno potrebnog da se maksimalno smanji utjecaj analitičke varijacije na biološku varijaciju

Editorial

Mauro Panteghini and Sverre Sandberg

Defining analytical performance specifications 15 years after the Stockholm conference

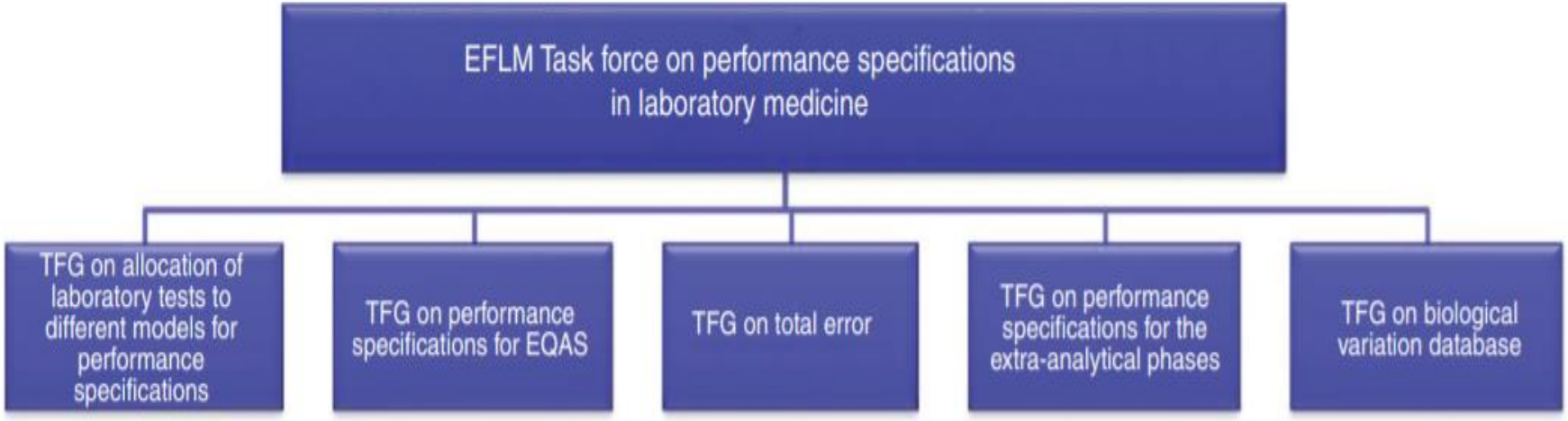


Figure 1: Structure of the EFLM task force on performance specifications in laboratory medicine.

Implementacija Milanskog sporazuma
1. Koji model odabrati?

DE GRUYTER

Clin Chem Lab Med 2017; 55(2): 189–194

Opinion Paper

Ferruccio Ceriotti*, Pilar Fernandez-Calle, George G. Klee, Gunnar Nordin, Sverre Sandberg, Thomas Streichert, Joan-Lluis Vives-Corrons and Mauro Panteghini, on behalf of the EFLM Task and Finish Group on Allocation of laboratory tests to different models for performance specifications (TFG-DM)

Criteria for assigning laboratory measurands to models for analytical performance specifications defined in the 1st EFLM Strategic Conference

Implementacija Milanskog sporazuma
1. Koji model odabrati?

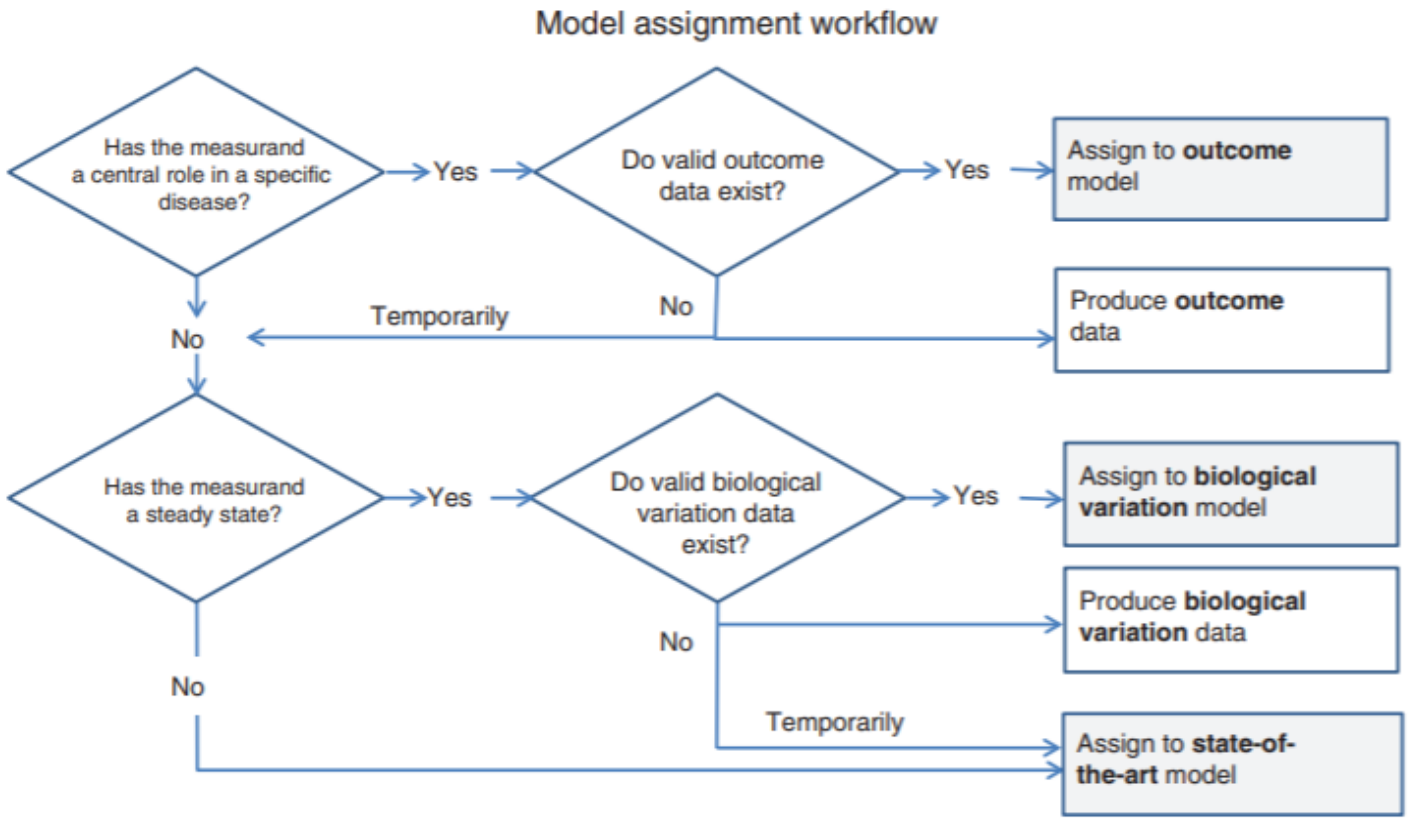


Figure 1: Workflow for assignment of a measurand to a defined analytical quality specification model.

Ceriotti et al.: Criteria for assigning measurands to models for analytical performance specifications. Clin Chem Lab Med 2017; 55(2): 189–194

Implementacija Milanskog sporazuma
1. Koji model odabrati?

Table 1: Proposal for assignment of some commonly requested laboratory measurands to the three models for analytical performance specifications (APS) as defined in the Milan Consensus.[a]

APS model 1: outcome-based	APS model 2: biological variation	APS model 3: state-of-the-ar
P-Cholesterol+ester	P-Sodium ion	U-Sodium ion
P-Cholesterol+ester in LDL	P-Potassium ion	U-Potassium ion
P-Cholesterol+ester in HDL	P-Chloride	U-Chloride
P-Triglycerides	P-Bicarbonate	U-Calcium ion
P-Glucose	P-Calcium ion	U-Magnesium ion
B-Hemoglobin A_{1c}	P-Magnesium ion	U-Phosphate (inorganic)
P-Albumin	P-Phosphate (inorganic)	U-Creatinine
P-Troponin T and P-troponin I	P-Creatinine	U-Urate
P-Thyrotropin	P-Cystatin C	
B-Hemoglobin	P-Urate	
B-Platelets	P-Proteins	
B-Neutrophil leukocytes	B-Erythrocytes	
	B-Erythrocyte volume fraction	
	B-Erythrocyte volume	
	P-Prothrombin time	
	P-activated partial thromboplastin time	

[a]Some of the measurands can also have APS from other models depending on their clinical use. P and B denotes the system blood plasma or whole blood, respectively. Measurements might be performed in different types of sample matrices, such as serum, heparin plasma, citrate plasma, etc., as appropriate for the method.

Ceriotti et al. Clin Chem Lab Med 2017; 55(2): 189–194

Implementacija Milanskog sporazuma
2. Definiranje granica prihvatljivosti

- Za sada ne postoji međunarodni konsenzus o definiranju granica prihvatljivosti kvalitete analitičke izvedbe za predloženi Model 1 i Model 3.
- Za definiranje granica prihvatljivosti za Model 2 temeljen na veličini biološke varijacije postoji konsenzus o definiranju granica prihvatljivosti za preciznost, bias i ukupnu analitičku pogrešku, a prvi korak je odabir poželjnih, optimalnih ili minimalnih ciljnih vrijednosti kvalitete izvedbe

Odabir razine kvalitete za preciznost

Personal View *Ann Clin Biochem* 1997; **34**: 8–12

Proposals for setting generally applicable quality goals solely based on biology

Callum G Fraser, Per Hyltoft Petersen[1], Jean-Claude Libeer[2] and Carmen Ricos[3]
From the Directorate of Biochemical Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK, [1]Clinical Chemistry Department, Odense University Hospital, Odense, Denmark, [2]Clinical Biology Department, Institute of Hygiene and Epidemiology, Brussels, Belgium, and [3]Clinical Biochemistry Department, University General Hospital, Vall d'Hebron, Barcelona, Spain

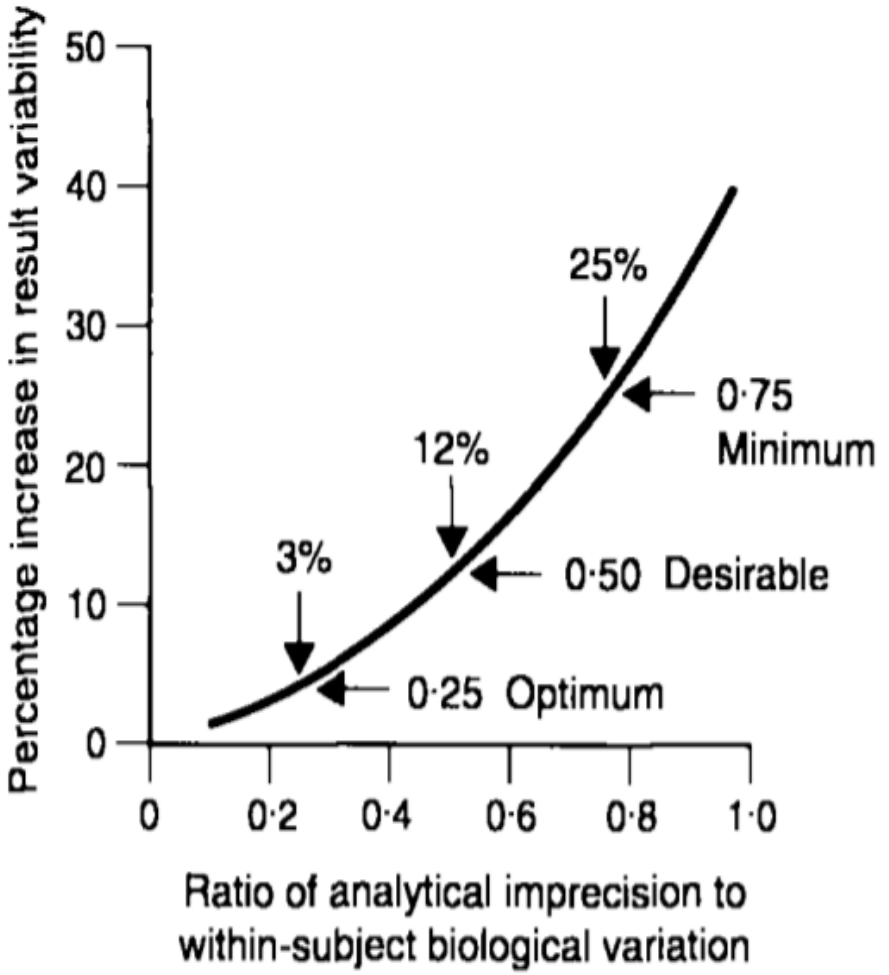


FIGURE 1. *The percentage increase in test result variability as a function of the ratio of analytical imprecision to within-subject biological variation.*

Fraser CG. et. al. Ann Clin Biochem 1997; 34:8-12

Odabir razine kvalitete za odstupanje od istinite vrijednosti (engl. bias)

Personal View *Ann Clin Biochem* 1997; **34**: 8–12

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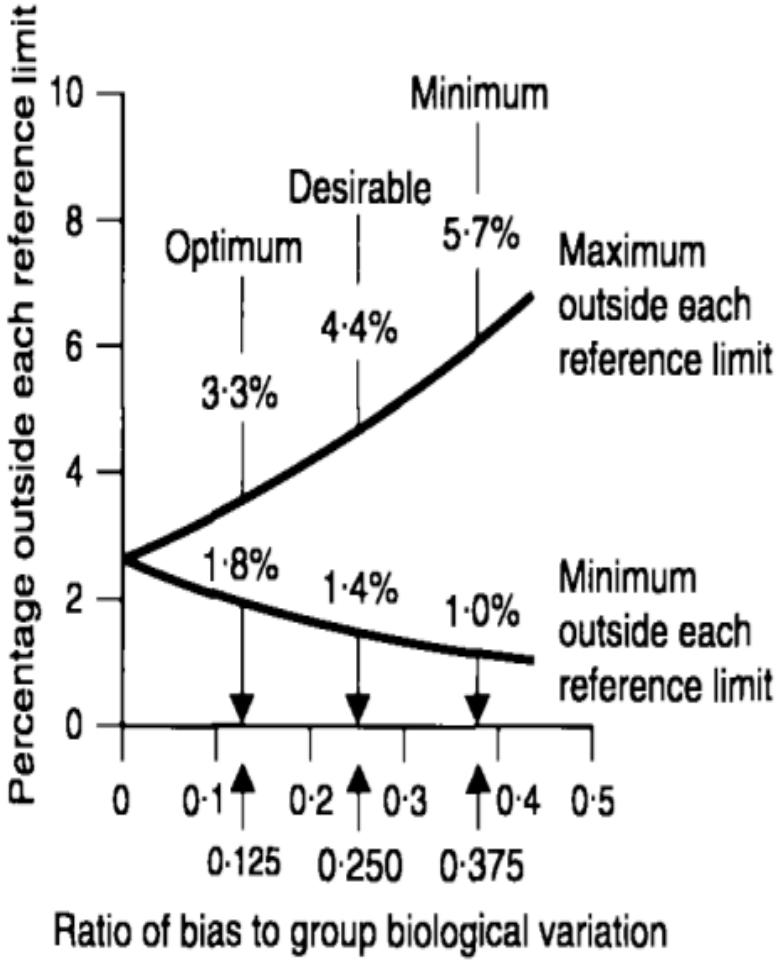
FIGURE 2. *The percentage increase in the population outside each reference limit as a function of the ratio of bias to group biological variation. A positive bias will increase the percentage outside the upper reference limit and decrease the percentage outside the lower reference limit. A negative bias will have the same effects but on the opposite reference limits.*



Fraser CG. et. al. Ann Clin Biochem 1997; 34: 8-12

Implementacija Milanskog sporazuma
Model 2 – odabir razine kvalitete izvedbe

Potrebno je odabrati razinu kvalitete izvedbe

APS	Optimum Performance	Desirable Performance	Minimum Performance
CVa	$0.25\ CV_w$	$0.5\ CV_w$	$0.75\ CV_w$
Bias	$0.125(CV_w^2+CV_G^2)^{1/2}$	$0.250(CV_w^2+CV_G^2)^{1/2}$	$0.375(CV_w^2+CV_G^2)^{1/2}$
TEa	Bias + 1.65 x CVa		

1/2 1/2 1/2

Implementacija Milanskog sporazuma Model 2- Optimalne ciljne vrijednosti

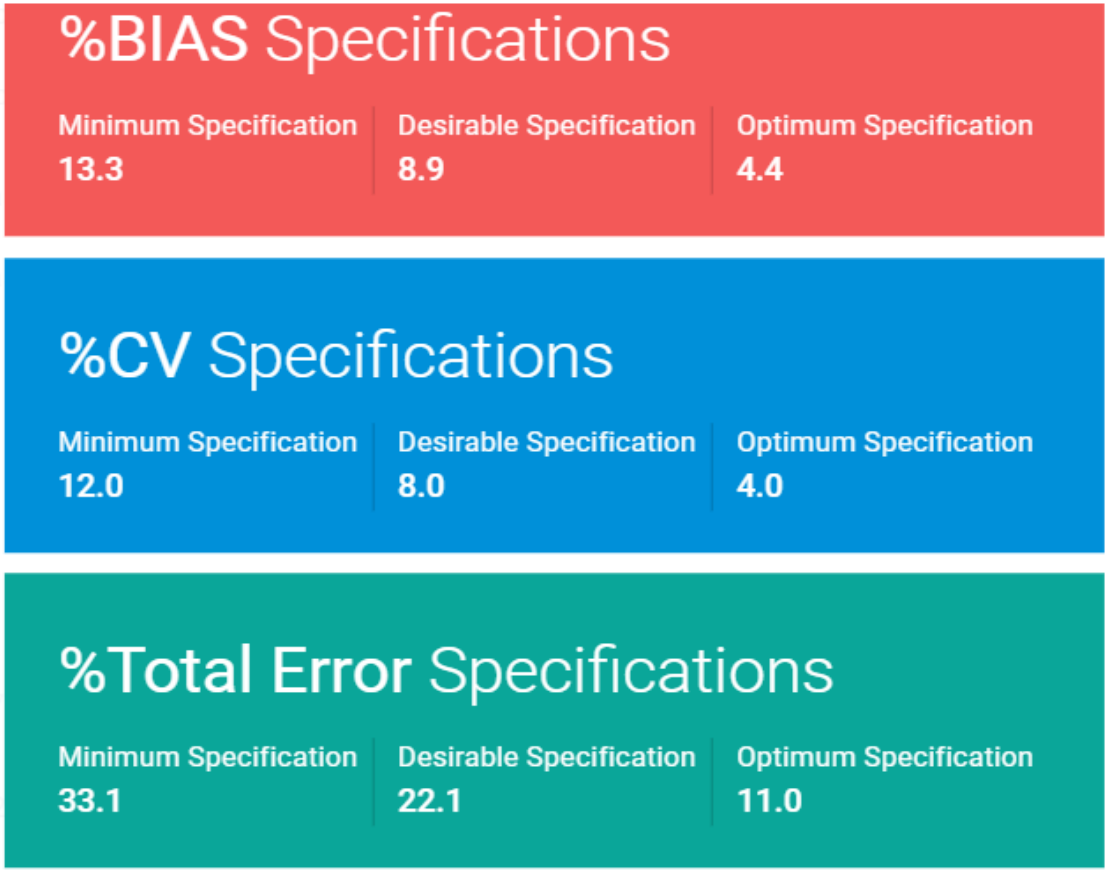
- za analite koji imaju veliku biološku varijaciju, a primjenjuju se analitičke metode za koje su tehnološki i metodološki uvjeti osigurali nisku analitičku varijaciju
- Primjer: kreatin kinaza

ID	Measurand		BV Estimate	median CV estimate	lower CI limit	higher CI limit	Date Updated	Tools
935	Creatine Kinase	Serum/plasma	Within-subject	16.0	15.4	29.5	2020-03-31 18:14:50 UTC	RCV
936	Creatine Kinase	Serum/plasma	Between-subject	31.8	25.7	41.5	2020-03-31 18:14:51 UTC	APS

https://biologicalvariation.eu/meta_calculations

Implementacija Milanskog sporazuma Model 2 - Optimalne ciljne vrijednosti

- Primjer: kreatin kinaza



https://biologicalvariation.eu/meta_calculations

Implementacija Milanskog sporazuma
Model 2 - Poželjne ciljne vrijednosti

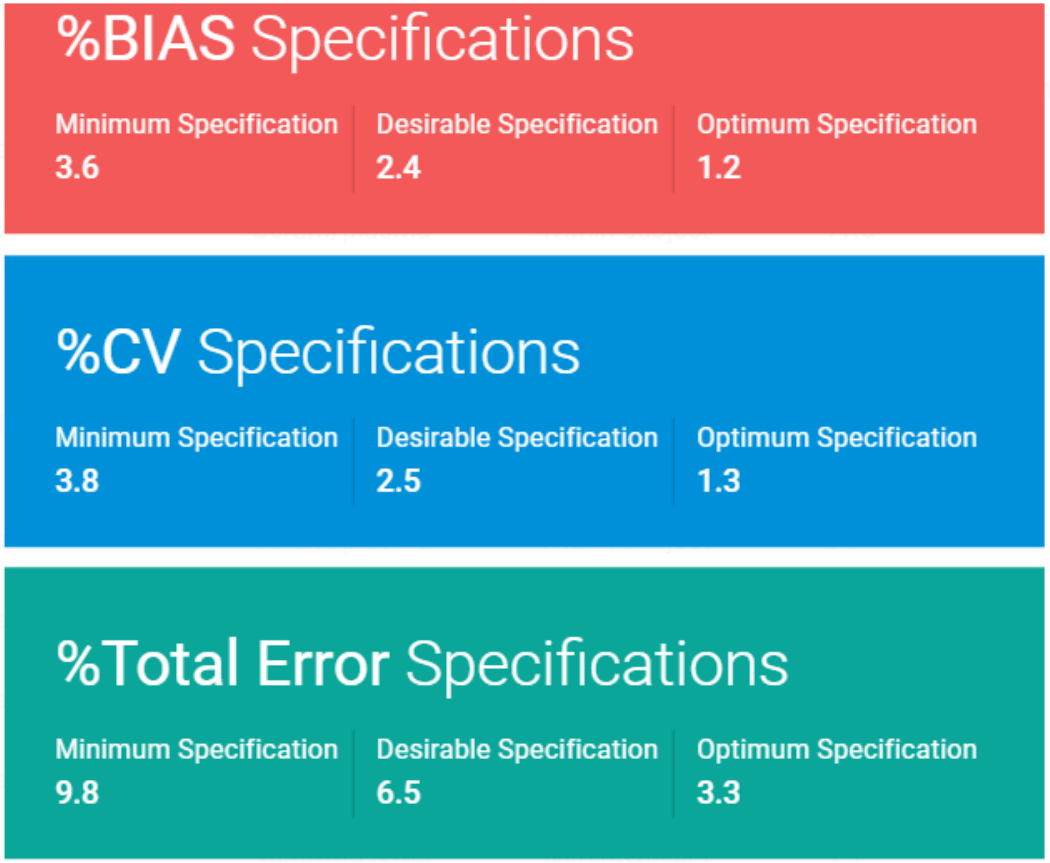
- Ovisno o veličini intra- i interindividualne biološke varijacije, a uvažavajući postojeće analitičke metode i tehnološke mogućnosti
- Primjer: glukoza

ID	Measurand		BV Estimate	median CV estimate	lower CI limit	higher CI limit	Date Updated	Tools
997	Glucose	Serum/plasma	Within-subject	5.0	4.1	12.0	2020-03-31 18:15:40 UTC	RCV
998	Glucose	Serum/plasma	Between-subject	8.1	2.7	10.8	2020-02-24 19:27:03 UTC	APS

https://biologicalvariation.eu/meta_calculations

Implementacija Milanskog sporazuma Model 2 - Poželjne ciljne vrijednosti

- Primjer: glukoza



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Implementacija Milanskog sporazuma Model 2 - Minimalne ciljne vrijednosti

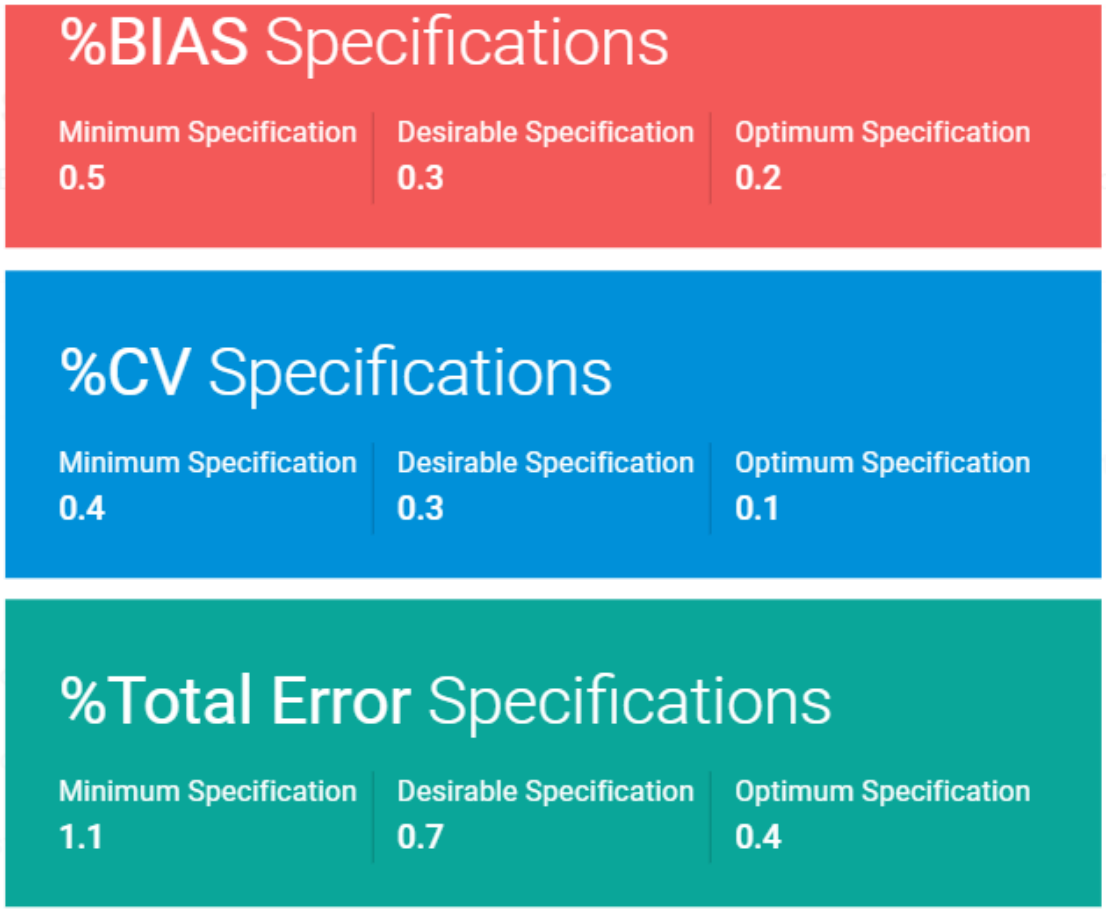
- za analite koji imaju malu biološku varijaciju, a postojećom tehnologijom i metodologijom ne mogu postići poželjne ciljne vrijednosti
- Primjer: natrij

ID	Measurand		BV Estimate	median CV estimate	lower CI limit	higher CI limit	Date Updated	Tools
973	Sodium	Serum/plasma	Within-subject	0.5	0.2	1.1	2020-03-31 18:15:12 UTC	RCV
974	Sodium	Serum/plasma	Between-subject	1.1	0.5	1.4	2020-03-31 18:15:13 UTC	APS

https://biologicalvariation.eu/meta_calculations

Implementacija Milanskog sporazuma
Model 2 - Minimalne ciljne vrijednosti

- Primjer: natrij



https://biologicalvariation.eu/meta_calculations

Opinion Paper

Wytze P. Oosterhuis*, Hassan Bayat, David Armbruster, Abdurrahman Coskun, Kathleen P. Freeman, Anders Kallner, David Koch, Finlay Mackenzie, Gabriel Migliarino, Matthias Orth, Sverre Sandberg, Marit S. Sylte, Sten Westgard and Elvar Theodorsson

The use of error and uncertainty methods in the medical laboratory

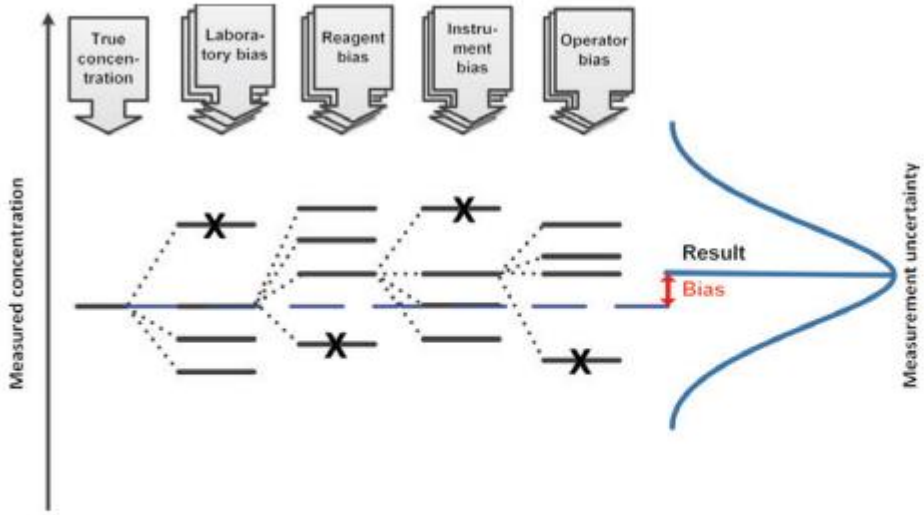


Figure 1: In the common situation where the samples of a particular patient are semirandomly allocated to different laboratories, reagents or reagent lots, measurement systems and operators, several bias components affecting the (hypothetical) true concentration value need to be considered and dealt with.
This randomness may be indistinguishable from imprecision.

Ciljevi analitičke kvalitete za mjernu nesigurnost

If for being acceptable, the degree of uncertainty (expanded) of a measurand in the clinical laboratory (including the accumulated uncertainty of the corresponding traceability chain) using unbiased assays should stay within $\pm 0.25\ CV_i$, $\pm 0.50\ CV_i$ or $\pm 0.75\ CV_i$ (optimum, desirable or minimum quality level, respectively), decisions need to be made on what proportion of this budget can be used up in the traceability chain to ensure enough budget is left for use in routine analysis. In the past, only the contribution of the uncertainty related to the reference procedures has been considered. In particular, Stöckl et al.

Bais et al.: Defining acceptable limits for the metrological traceability of specific measura Clin Chem Lab Med 2013; 51(5): 973–979

KOJI SU PRIHVATLJIVI UDJELI SASTAVNICA MJERNE NESIGURNOSTI REZULTATA LABORATORIJSKIH PRETRAGA U UVJETIMA MJERITELJSKE SLJEDIVOSTI?

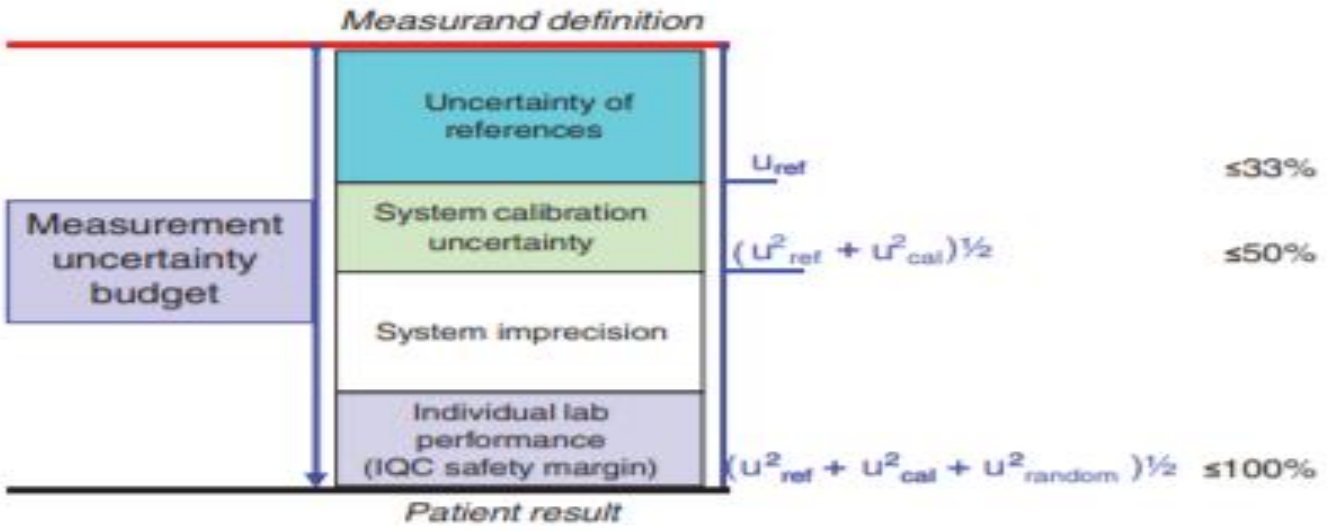


Figure 1: Recommended limits for sources of combined uncertainty budget (expressed as percentage of total budget uncertainty goal) in traceability implementation.
IQC, internal quality control.

Braga et al.: Performance criteria for combined uncertainty budget

Clin Chem Lab Med 2015; 53(6): 905–912

Table 1. Milan model allocation and recommended analytical performance specifications (APS) for standard measurement uncertainty (MU) on clinical samples and at higher-order reference level for the selected measurands.

		APS for standard MU on clinical samples, %[a]		Allowable standard MU for higher-order references, %[b]	
Measurand	APS model	Desirable	Minimum	Desirable	Minimum
B-Total hemoglobin	Outcome-based	2.80	4.20	0.93	1.40
P-Potassium	Biological variation	1.96	2.94	0.65	0.98
P-Sodium	Biological variation	0.27	0.40	0.09	0.13
P-Chloride	Biological variation	0.49	0.74	0.16	0.25
P-Alanine aminotransferase	Biological variation	4.65	6.98	1.55	2.33
P-C-reactive protein	State of the art	3.76	5.64	1.25	1.88
P-Glucose	Outcome-based	2.00	3.00	0.67	1.00
P-Creatinine	Biological variation	2.20	3.30	0.73	1.10
P-Urea	Biological variation	7.05	10.6	2.35	3.53
P-Total calcium	Biological variation	0.91	1.36	0.30	0.45
P-Total bilirubin	Biological variation	10.5	15.7	3.50	5.23
B-HbA_{1c}	Outcome-based	3.00	3.70	1.00	1.23
S-25-hydroxyvitamin D3	Outcome-based	10.0	15.0	3.33	5.00

B, blood; P, plasma; S, serum.
[a]Derived from (33).
[b]Estimated as one-third of APS for standard MU for clinical samples.

Panthegini M. et. al. Clin Chem. 2021;67:1590-1605

Ciljevi analitičke kvalitete u vanjskoj procjeni kvalitete

DE GRUYTER

Clin Chem Lab Med 2017; 55(7): 949–955

Opinion Paper

Graham R.D. Jones*, Stephanie Albarede, Dagmar Kesseler, Finlay MacKenzie, Joy Mammen, Morten Pedersen, Anne Stavelin, Marc Thelen, Annette Thomas, Patrick J. Twomey, Emma Ventura and Mauro Panteghini, for the EFLM Task Finish Group – Analytical Performance Specifications for EQAS (TFG-APSEQA)

Analytical performance specifications for external quality assessment – definitions and descriptions

Primjer kriterija analitičke izvedbe u vanjskoj procjeni kvalitete

Table 2: Example of summary description of analytical performance specifications (APS) based on the RCPAQAP General Serum Chemistry External Quality Assurance (EQA) Scheme.

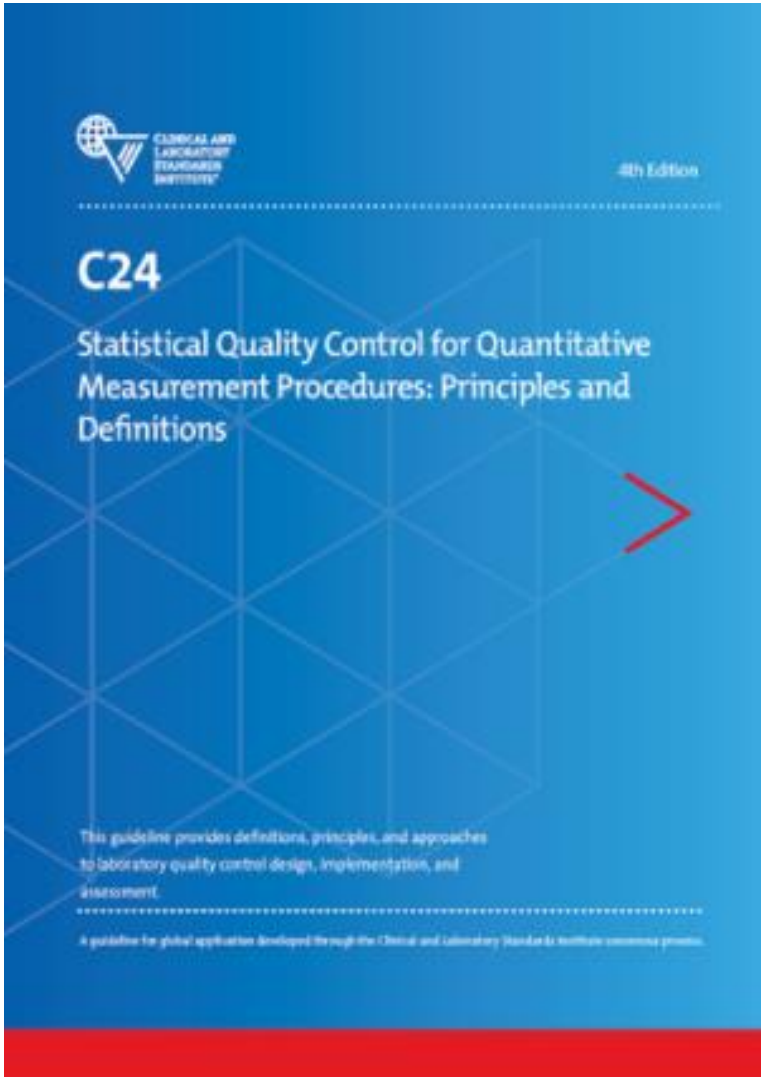
1. The EQA material is not validated as commutable
2. The overall target-setting method for each measurand is shown below. In addition, method, instrument, reagent manufacturer-based consensus targets are provided based on returned results
3. The APS are to be applied to each individual measurement result
4. The APS are applied for assessment of total error (i.e. the effects of imprecision and bias combined)
5. The rationale for the APS is 'Aspirational' (to improve performance) where this is required. The response of the laboratory to 'out of range' results should be to review performance and seek improvement
6. The APS are established based on biological variation and state of the art (levels 2 and 3 from Milan conference). The components of biological variation and the level (optimal, desirable, or minimal) are shown below

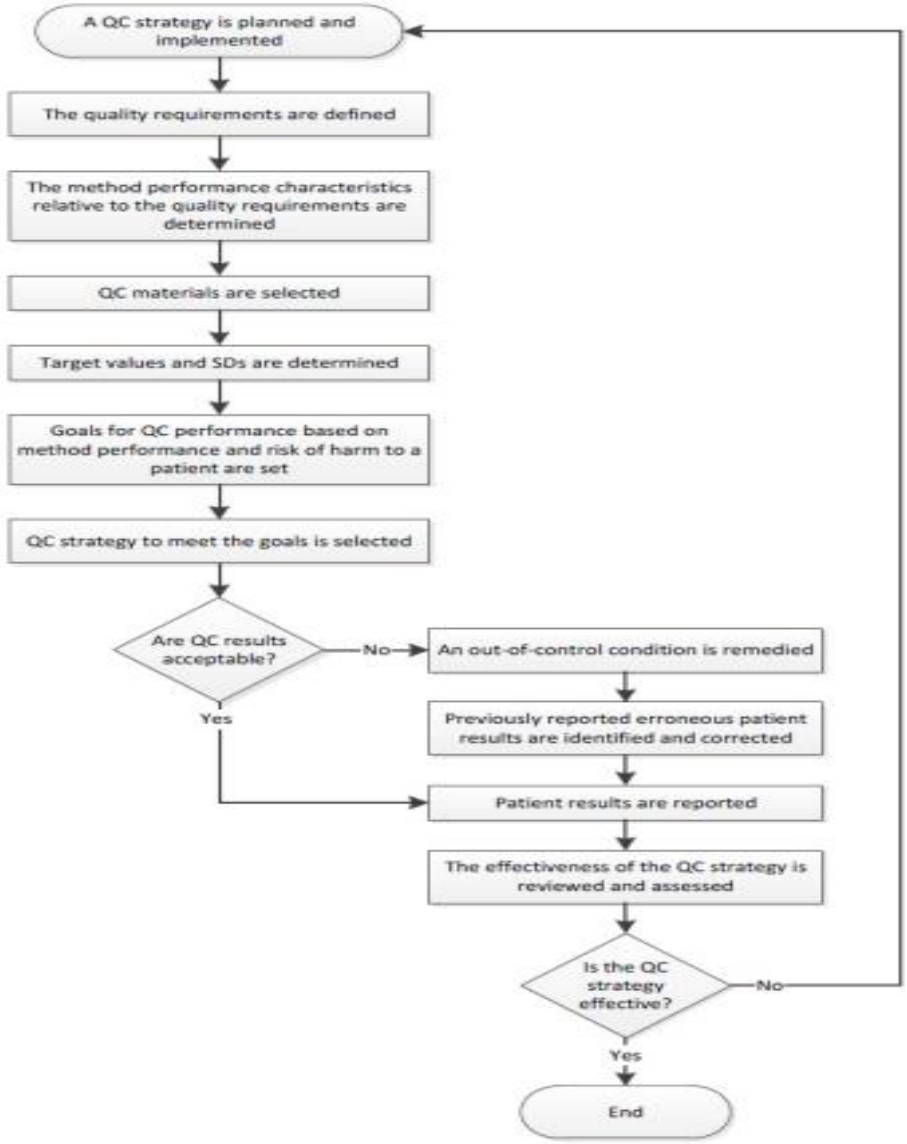
Further details on the RCPAQAP process used to establish these APS are available [9, 15]

Measurand	Assignment of target	Analytical performance specifications	Employed component(s) of biological variation	Quality level
S/P-ALT	IFCC reference procedure in a JCTLM-listed reference laboratory	±5 U/L up to 40 U/L; ±12% >40 U/L	Within-individual (imprecision)	Optimal
S/P-Bicarbonate	Selected well-controlled commercial measuring system by an ISO 15189 accredited clinical laboratories	±2.0 mmol/L up to 20.0 mmol/L; ±10% >20.0 mmol/L	Within- and between-individual (total error)	Minimal
S-Transferrin	Median of laboratories participating in EQA	±0.20 g/L up to 2.50 g/L; ±8% >2.50 g/L	Within- and between-individual (total error)	Minimal

Clin Chem Lab Med 2017; 55(7): 949–955

Praktična rješenja za upravljanje analitičkom kvalitetom na temelju rizika



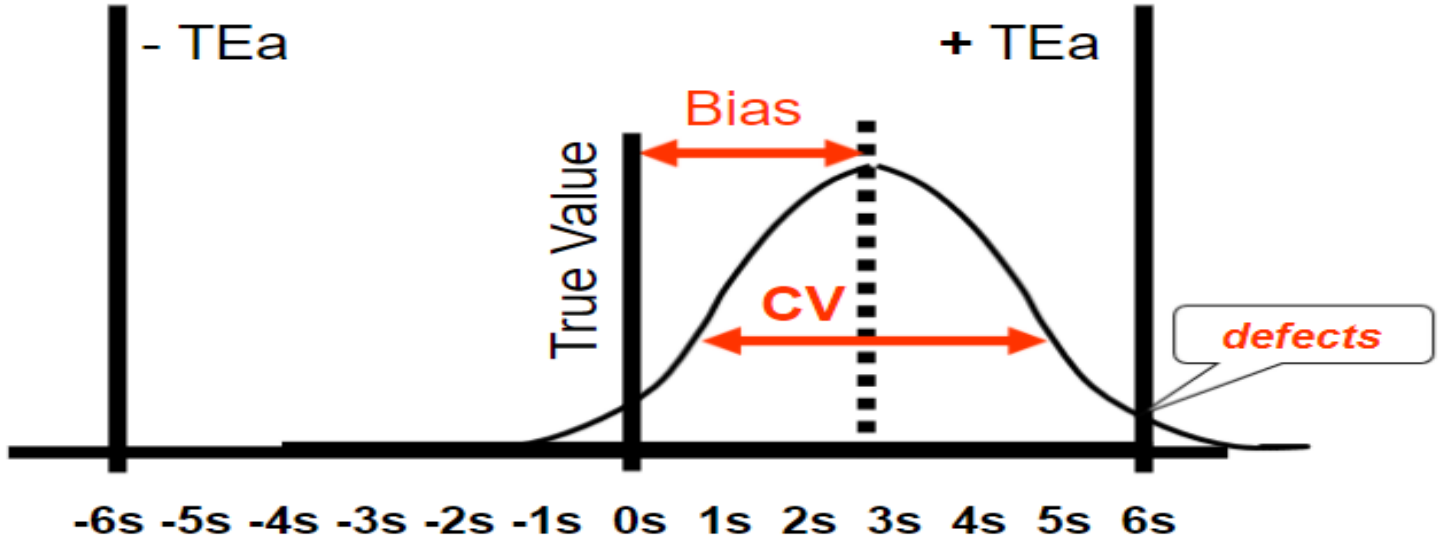


Praktična rješenja za upravljanje analitičkom kvalitetom na temelju rizika

WESTGARD QC

SIGMA METRIC EQUATION FOR ANALYTICAL PROCESS PERFORMANCE

$$\text{Sigma-metric} = (TE_a - |\text{Bias}|)/CV$$

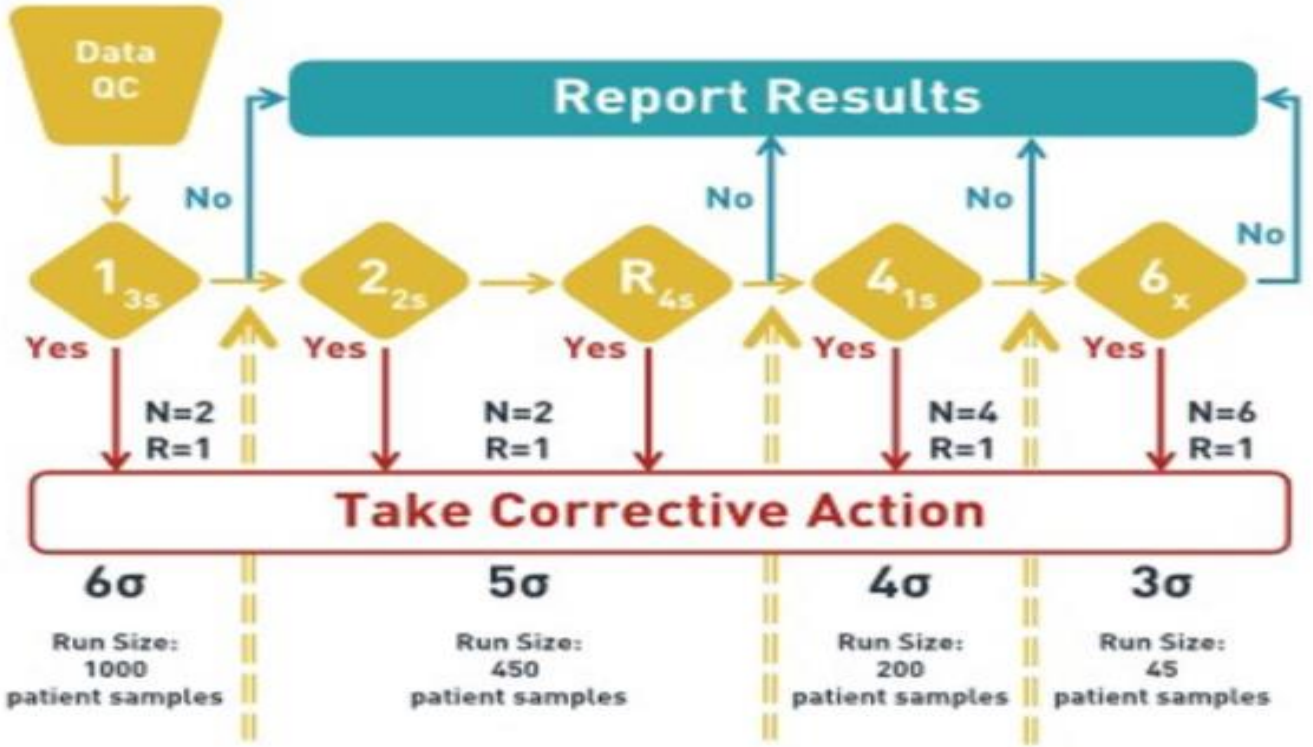


WWWWWWWWWQC

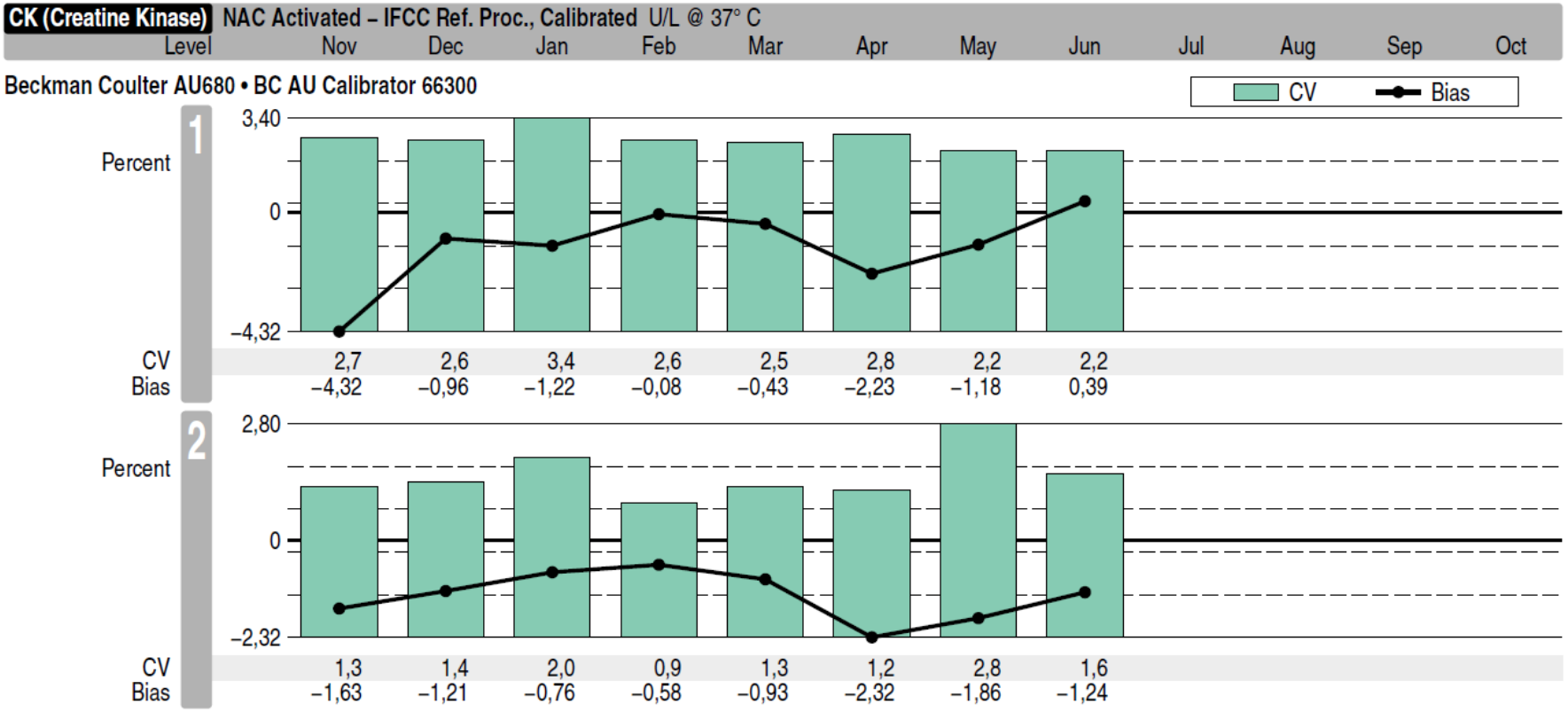
Praktična rješenja za upravljanje analitičkom kvalitetom na temelju rizika

WESTGARD QC

THE 'NEW' "WESTGARD RULES"?



Praktična rješenja za upravljanje analitičkom kvalitetom: Međulaboratorijske usporedbe unutarnje kontrole kvalitete



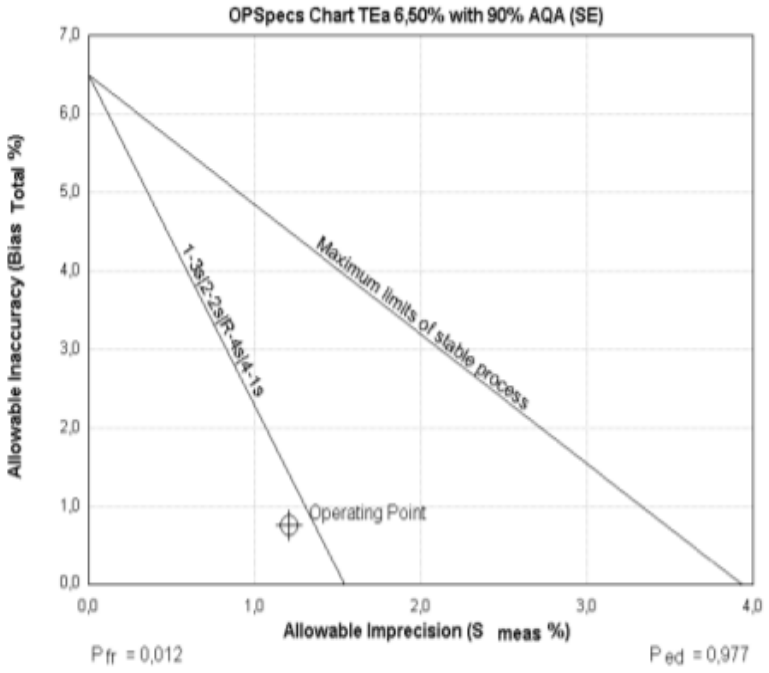
Informatička rješenja za izbor i primjenu optimanih kontrolnih pravila i broja kontrolnih uzoraka

Bio-Rad Westgard Advisor Report

Lab 179443	**Assayed Chemistry**	**Lot 26460**
KLINICKA BOLNICA MERKUR	Date Printed: 3-12-2021-	Lot Exp: 31-7-2022-

Glucose (mmol/L)

Instrument:	Beckman Coulter AU680	Total Allowable Error (TEa):	6,50
Method:	Hexokinase	Bias %:	0,772
Reagent:	Dedicated Reagent	CV:	1,21
TEa Selection:	BV Des bias/ Des imprecision	Sigma:	4,73
Lab Data Range:	1.1.2020. - 1.12.2021.	Number of Control Measurements (N):	2
Group:	Peer Cumulative	Probability of False Rejection (Pfr):	0,012
Detection Level:	(AQA Level >= 90%)	**Suggested Rules: 1-3s|2-2s|R-4s|4-1s**	



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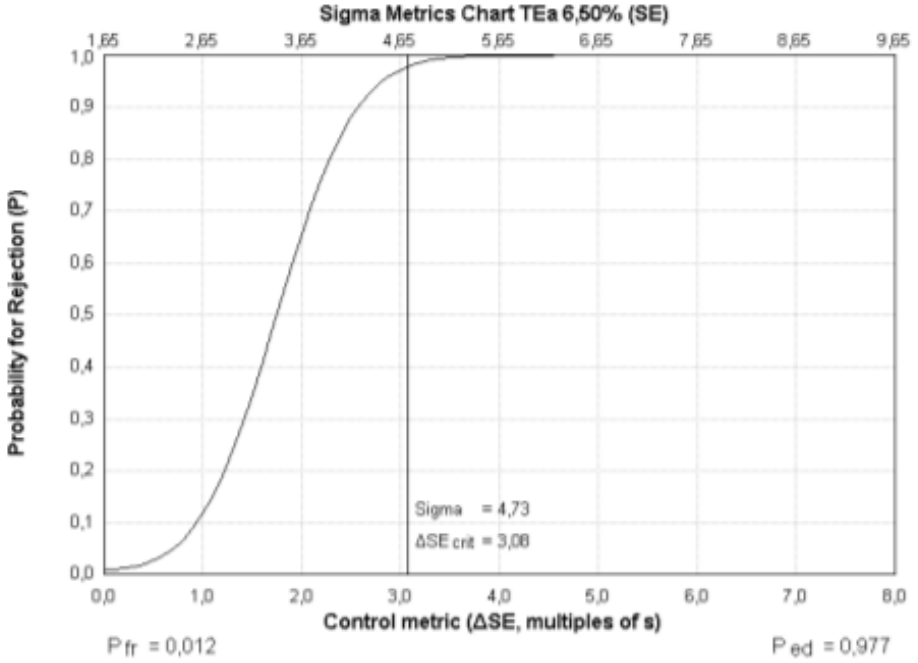
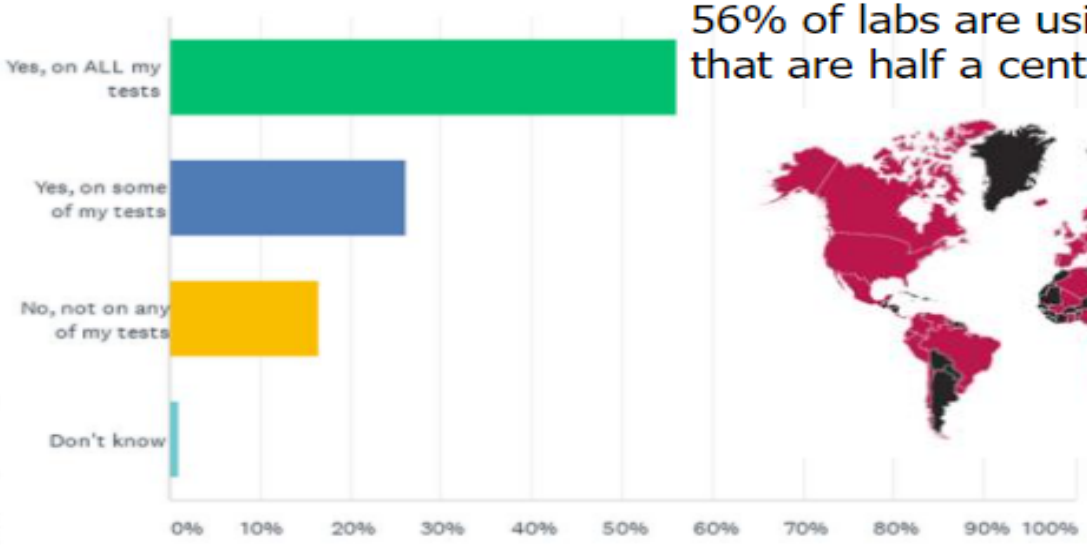


WESTGARD QC

CURRENT GLOBAL QC SURVEY
(>500 LABS >100 COUNTRIES)

Q8 Do you use a single range (example: 2 SD limits) for your assays to accept or reject runs?



56% of labs are using QC rules that are half a century old!

WESTGARD QC

WHY DEFY THE 2 SD CONVENTION?

2 SD control limits have high false rejection rates built into them.

- **9% for 2 controls,**
- **14% for 3 controls**

50 years ago, this was acceptable.

Given the surge in menu, in volume, in instrument engineering, do we really want to have 1 of every 10 runs be falsely rejected?

Zaključak

- Potrebno je definirati stupanj kvalitete potreban za namjeravanu upotrebu i veličinu pogreške koja se može toleritati bez ugrožavanja sigurnosti bolesnika
- Model ukupne dopuštene pogreške i njegova integracija sa pristupom šest sigma pružili su praktičan pristup s korisnim alatima i tehnikama za mjerenje, praćenje i poboljšanje analitičke kvalitete
- Mjerna nesigurnost važna je za definirranje prikladnosti testa, za provjeru kvalitete IVD proizvoda, te je medicinski laboratoriji trebaju procjeniti i potvrditi na razini rezultata pacijenta